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Attorney Docket No.: 3298.1

## REMARKS

Applicants have amended Claims 14, 39, 64 and 90. Support for the amendments to Claims 14 and 90 may be found, for example, on pages 10 (lines 12-13) and 29 (lines 9-10) of the Specification. Applicants submit that no new matter is entered by these amendments and respectfully request entry of the same.

### *A. General*

The Examiner has pointed out discrepancies between the marked-up copy of the Claims, the "Current version of the whole Claim set" (both of which were submitted in the amendment filed 5/9/03) and the currently-pending claims. Applicants would like to clarify that Claim 100 was erroneously numbered as Claim 101 in the marked-up copy, and concur with the Examiner's assertion that the clean copy of the amended claims is the binding version/ version under examination.

### *B. Objections to the Specification/ Drawings are Obviated*

The Examiner alleges that the proposed drawing correction to Figure 6 introduces new matter into the drawing. Applicants respectfully disagree. Support for the proposed correction may be found, for example, on pages 25 and 32 (lines 6-9) of the Specification, which describe examples involving standard hypothesis testing (one-tailed test) utilizing the null hypothesis ( $H_0$ ) and the alternative hypothesis ( $H_1$ ). It would also be evident to one of ordinary skill in the art that if, for example,

$\mu = 0$  is the Null Hypothesis  $H_0$ ,

$\mu > 0$  would be the Alternative Hypothesis, which would be denoted as  $H_1$

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Thus, one of ordinary skill in the art would recognize that in Figure 6 the alternative hypothesis was erroneously labeled as  $H_0$  instead of  $H_1$ . Applicants therefore submit that the amendment of Figure 6 does not present new matter.

The Examiner objects to the amendment filed on 5/9/03 under 35 U.S.C. § 132 because it allegedly introduces new matter. Specifically, the Examiner has objected to the amendment because it allegedly changes formulas throughout the Specification, Figure 6 and the Claims without proper support. Applicants provide the following explanation and support for the various changes:

	Portion Amended (by Amendment filed on 5/9/03)	Support and/ or explanation
Specification	Page 4 (lines 10-18) $MM_1 \rightarrow MM_i$	Support may be found, for example, in the initial portion of the same sentence
	Page 5 (lines 12-15) $\text{median}((PM_i - MM_i)/(PM_i - MM_i))$ $\rightarrow$ $\text{median}((PM_i - MM_i)/(PM_i + MM_i))$	Support may be found, for example, on page 10 (lines 12-13), page 29 (lines 6-10) and Figure 6.  One of ordinary skill in the art would recognize that a typographical error is present in view of the above-cited support and would recognize that the Applicants' correction was obvious.
	Page 7 (lines 11-16) $\text{median}((PM_i - MM_i)/(PM_i - MM_i))$ $\rightarrow$ $\text{median}((PM_i - MM_i)/(PM_i + MM_i))$	Support may be found, for example, on page 10 (lines 12-13), page 29 (lines 6-10) and Figure 6.  One of ordinary skill in the art would recognize that a typographical error is present in view of the above-cited support and would recognize that the Applicants' correction was obvious.
	Page 29 (lines 3-12) $H_1: \text{median}(PM_i - MM_i)/(PM_i - MM_i) > \tau_2 \rightarrow$	Support may be found in the preceding formula for $H_0$ . In a one-tailed hypothesis, the formulae for $H_0$ and $H_1$ are the same and the

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	$H_1: \text{median}(PM_i - MM_i) / (PM_i + MM_i) > \tau_2$	typographical error and resultant correction would thus be obvious to one of ordinary skill in the art.
<b>Claims</b>	Claims 29 and 67 (subscript changed from '1' to '3') for example, $\tau_{[1]3} = c_{[1]3} \sqrt{\text{median}(PM_i)}$ , and $c_{[1]3}$	Page 31
	Claim 52 $\text{median}(PM_i - MM_i) / (PM_i - MM_i)$ → $\text{median}(PM_i - MM_i) / (PM_i + MM_i)$	Support may be found, for example, on page 10 (lines 12-13), page 29 (lines 6-10) and Figure 6.  One of ordinary skill in the art would recognize that a typographical error is present in view of the above-cited support and would recognize that the Applicants' correction was obvious.
<b>Figures</b>	Figure 6	See explanation on page 3

**C. Claim Rejections under 35 U.S.C. § 112 should be withdrawn**

Claims 1-9, 11-21, 23-34, 36-47, 49-59, 61-72, 74-85, 87-97 and 99-103 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing new matter and for alleged lack of enablement. Applicants respectfully disagree with the Examiner.

The Examiner alleges that the Applicants amended formulas in the Specification, Figure 6 and Claims without providing bases for these changes. Applicants have provided detailed explanations for all the changes in Section B of this paper and request that the rejection be withdrawn in view of the same.

The Examiner alleges that no basis was provided for newly introduced Claim 103. Applicants submit that support for the newly introduced claim may be found, for example, on page 34 (lines 12-14) of the Specification.

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The Examiner has rejected Claims 1, 26, 39, 64, 77 and 91-103 on the basis that the Specification does not provide guidance on selecting/ developing other test statistics for use in the claimed method nor the associated threshold values. Applicants respectfully disagree with the Examiner. The specification provides several examples of selecting/ developing other test statistics including simple difference between perfect match intensities and mismatch intensities (e.g. page 24) or variations such as the Ryder's discrimination score. Applicants respectfully submit that it is well within the skill of an ordinary artisan to develop additional suitable statistics (variations that indicate the intensity difference) without undue experimentation.

Claims 1-2, 6-9, 11-12, 14-15, 26-27, 31-34, 36-40, 44-47, 49-53, 56-69, 61-65, 69-72, 74-78, 82-85, 87-91 and 93-103 are rejected for allegedly requiring a threshold value without reciting how it is determined or its value. Applicants respectfully submit that like other statistical tests, a threshold value is determined based upon among other things, the stringency requirement. Determining appropriate threshold values for statistical tests is well within the capabilities of one of ordinary skill in the art.

The Examiner also alleges that many of the claims allegedly do not require a particular significance level for the  $p$ -value to determine the presence or absence of a transcript. Applicants respectfully disagree and would like to draw the Examiner's attention to at least Claims 6, 9, 12, 18, 21, 24, which provide very specific guidance on the presence/ absence of a transcript is present depending on the significance level for the  $p$ -value.

Claims 14-21, 23-25, 39-47, 49-51, 52-59, 61-72 and 74-76 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically,

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Claims 14 and 90 are rejected for reciting an allegedly erroneous formula  $median((PM-MM_i)/(PM+MM_i))$ . Applicants have amended Claims 14 and 90 in order to correct the formula. Support for the amendment may be found, for example, on pages 10 (lines 12-13) and 29 (lines 9-10) of the Specification. Applicants submit that no new matter is entered by this amendment and respectfully request entry of the same.

Claims 39 and 64 are allegedly confusing in reciting "a computer readable media for storing said computer program codes" as the language allegedly does not make clear if the computer readable media is actually storing the code. Applicants have amended Claims 39 and 64 to recite "a computer readable medium that stores said computer program codes" and request that this rejection of Claims 39 and 64 be withdrawn.

With regard to Claims 39 and 64, the Examiner seeks clarification with respect to whether the software product of the preamble is an integrated product where the results of one program code are used as input for the next program code or whether these are three discrete pieces of software. Applicants respectfully submit it would be obvious to one of ordinary skill in the art that the computer program codes represent three components of the integrated software product.

In summary, Applicants respectfully submit that for the above reasons, the claim rejections under 35 U.S.C. § 112 should be withdrawn.

***D. Claim Rejections under 35 U.S.C. § 103 should be withdrawn***

Claims 1, 39 and 77 are rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over Lockhart et al. (1996) in view of either Hogg et al. or Hollandcr et al.

Applicants, in the previous response, submitted that there was no teaching, suggestion or motivation in the cited references that non-parametric tests are suitable for

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analyzing probe level data. The Examiner alleges that nonparametric statistics would have been well known in the nucleic acid arts and expression analysis with respect to differences in signal intensity. The Examiner cited three references to support her position.

Lynch et al. (U.S. Patent No. 5,998,139, at column 9, lines 44-51) discusses the use of unpaired Mann-Whitney U test for determining standard deviations for expression density differences between different groups of animals. Chartier-Harlin et al. (US Patent No. 6,391,553 at column 8, lines 38-53) discusses the Mann-Whitney nonparametric test for the significance of the changes of gene expression in patients with Alzheimer's disease. It is related to how a specific gene responds to a disease state, rather than nucleic acid probe characteristics. Kargman et al., (U.S. Patent No. 6,593,361, at column 15, line 67, through column 16, line 30) discusses using Mann-Whitney test for protein levels of PGH-1 and PGHS-2 in normal and tumor cells. Again, this cited reference does not provide any suggestion or teaching about the nonparametric characteristics of nucleic acid probe hybridization signal. In contrast, the rejected Claims recite a method for detecting whether a transcript is present in a sample, providing perfect match and mismatch probes. The nonparametric tests are applied to determine whether a gene is detectable in a tissue based upon the probe intensities. Applicants respectfully submit that the Examiner has failed to present any evidence that those of ordinary skill in the art would have understood the applicability of nonparametric statistics for analyzing probe level data to determine whether a transcript is present in a sample.

Therefore, the rejection of claims under 35 USC §103 should be withdrawn.

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## CONCLUSION

For these reasons, Applicants believe the application is now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

If the Examiner has any questions pertaining to this application, the Examiner is requested to contact the undersigned agent.

Respectfully submitted,



Priyadarshini Rath  
Limited Recognition under 37 CFR 10.9(b)

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